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(54) Title: PHARMACEUTICAL FORMS OF EPOTHILONES FOR ORAL ADMINISTRATION

(57) Abstract: The invention relates to methods of increasing the bioavailability of orally administered epothilones. Epothilones administered by the methods of the invention are sufficiently bioavailable to have a pharmacological effect. The invention further relates to pharmaceutical compositions, pharmaceutical dosage forms, and kits for use in the methods of the invention.

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Table 5. Summary of Pharmacokinetics of Patients Administered Compound A Orally and Intravenously

Dose (mg/m ²)	20		25		30	
N	3		11		4	
Route	IV	Oral	IV	Oral	IV	Oral
Formulation	IV	Solution for Oral Admin.	IV	Solution for Oral Admin.	IV	Solution for Oral Admin.
C _{MAX} ^a (ng/mL)	251 (108)	142 (106)	447 (189)	180 (110)	711 (530)	274 (104)
T _{MAX} ^b (h)	0.25 (0.25, 0.25)	1.0 (0.25, 1.50)	0.50 (0.25, 0.50)	0.50 (0.25, 3.00)	0.50 (0.25, 0.50)	0.50 (0.25, 0.75)
AUC(0-T) ^{a,c} (h.ng/mL)	796 (587)	404 (381)	848 (284)	533 (284)	1155 (292)	708 (291)
% F ^a	NA	43.5 (16.1)	NA	55.6 (18.4)	NA	62.2 (25.1)

^aMean(SD)

^bMedian (min, max)

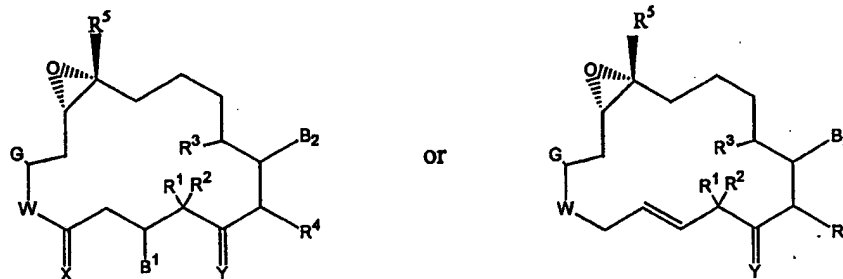
^cRepresents AUC(0-T)

The embodiments of the invention described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

The Claims

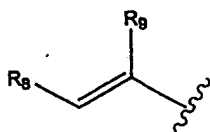
What is claimed is:

1. A method of increasing the bioavailability of orally administered
 5 epothilones comprising orally administering to a human one or more epothilones of
 Formula:

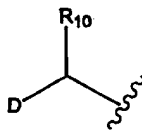


wherein:

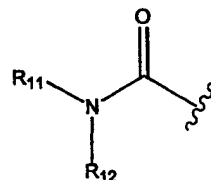
- G is selected from the group consisting of alkyl, substituted alkyl, aryl,
 10 substituted aryl, heterocyclo,



(a)



(b)



(c)

- W is O or NR₁₆;
- 15 X is O; S; CHR₁₇; or H, R₁₈;
- Y is selected from the group consisting of O; H, H; H, OR₂₂; OR₂₃, OR₂₃;
 NOR₂₄; H, NOR₂₅; H, HNR₂₆R₂₇; NHNR₂₈R₂₉; H, NHNR₃₀R₃₁ or CHR₃₂, where
 OR₂₃, OR₂₃ can be a cyclic ketal;
- B₁ and B₂ are selected from the group consisting of H, OR₃₃, OCOR₃₄,
 20 OCONR₃₅R₃₆, NR₃₇R₃₈, or NR₃₉CONR₄₀R₄₁;
- D is selected from the group consisting of NR₄₂R₄₃ or heterocyclo;

R₁, R₂, R₃, R₄, and R₅ are selected from H, lower alkyl;

R₈, R₉, R₁₀ and R₁₁ are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo or substituted heterocyclo;

5 R₁₇, R₁₈, R₂₂, and R₂₃ are selected from the group consisting of H, alkyl, and substituted alkyl;

R₂₄, R₂₅, R₂₆, R₂₈, R₃₀, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₃₉, R₄₀, R₄₁, R₄₂, R₅₁, R₅₂, R₅₃, and R₆₁ are selected from the group of H, alkyl, substituted alkyl, aryl or substituted aryl;

10 R₁₂, R₁₆, R₂₇, R₂₉, R₃₁, R₃₈, and R₄₃, are selected from the group consisting of H, alkyl, substituted alkyl, substituted aryl, cycloalkyl, heterocyclo, R₅₁C=O, R₅₂OC=O, R₅₃SO₂, hydroxy, and O-alkyl or O-substituted alkyl, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof, and orally administering one or more pharmaceutically acceptable acid
15 neutralizing buffers.

2. The method of claim 1, wherein the pharmaceutically acceptable acid neutralizing buffer is administered concurrently with the epothilone.

20 3. The method of claim 1, wherein the pharmaceutically acceptable acid neutralizing buffer is administered before the epothilone.

4. The method of claim 3, wherein the pharmaceutically acceptable acid neutralizing buffer is administered not more than about 1 hour before the epothilone.

25

5. The method of claim 1, wherein the pharmaceutically acceptable acid neutralizing buffer is administered after the epothilone.

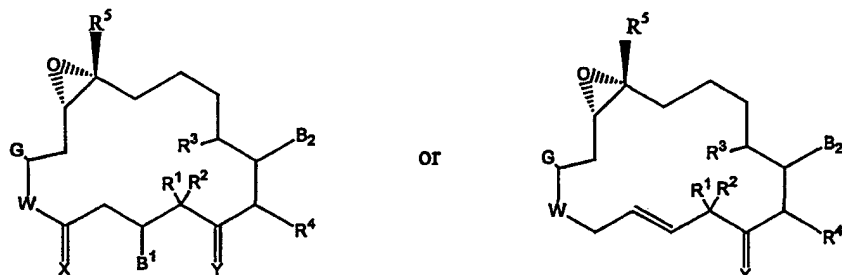
6. The method of claim 5, wherein the pharmaceutically acceptable acid
30 neutralizing buffer is administered not more than about 1 hour after the epothilone.

7. The method of claim 1, wherein the pharmaceutically acceptable acid neutralizing buffer is administered before and after the epothilone.
8. The method of claim 7, wherein the pharmaceutically acceptable acid neutralizing buffer is administered not more than about 1 hour before and not more than about 1 hour after the epothilone is administered.
9. The method of claim 1, wherein the pharmaceutically acceptable acid neutralizing buffer is administered in an amount sufficient to deliver at least about 20 milliequivalents of acid neutralization capacity.
10. The method of claim 1, wherein the pharmaceutically acceptable acid neutralizing buffer is administered as an aqueous solution having a pH of between about 5 to 9.
11. The method of claim 1, wherein the pharmaceutically acceptable acid neutralizing buffer is administered as an aqueous solution comprising anhydrous dibasic sodium phosphate, sodium citrate dihydrate, and anhydrous citric acid.
12. The method of claim 11, wherein the pH of the aqueous solution is about 7.
13. The method of claim 1, wherein the bioavailability of the one or more epothilones or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof is at least about 20 percent.
14. The method of claim 1, wherein the one or more epothilones or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof is orally administered as a solution in propylene glycol and ethanol, wherein the in ratio of propylene glycol:ethanol is about 80:20.

15. The method of claim 1, wherein the one or more epothilones or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof is administered in a total amount of about 0.05 to about 200 mg/kg/day.
- 5 16. The method of claim 15, wherein the one or more epothilones of or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof is administered in about 2 to 4 divided doses.
- 10 17. The method of claim 1, wherein the epothilone is [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 16S*]]-7, 11-dihydroxy 8, 8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl-17-oxa-4-azabicyclo[14.1.0]heptadecane-5, 9-dione.
18. The method of claim 1 comprising:
- 15 (a) orally administering an aqueous solution of a pharmaceutically acceptable acid neutralizing buffer comprising anhydrous dibasic sodium phosphate, sodium citrate dihydrate, and anhydrous citric acid;
- (b) orally administering the one or more epothilones or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof as a solution of propylene glycol; and
- 20 (c) orally administering an aqueous solution of a pharmaceutically acceptable acid neutralizing buffer comprising anhydrous dibasic sodium phosphate, sodium citrate dihydrate, and anhydrous citric acid;.
19. The method of claim 18, wherein the epothilone is [1S-[1R*, 3R*(E), 7R*, 25 10S*, 11R*, 16S*]]-7, 11-dihydroxy 8, 8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl-17-oxa-4-azabicyclo[14.1.0]heptadecane-5, 9-dione.

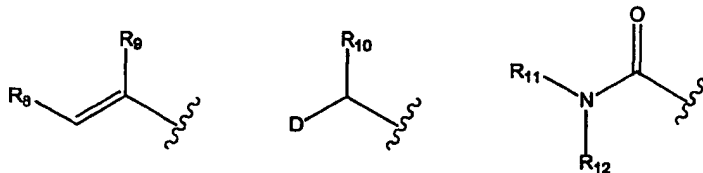
20. A kit for use in a method of increasing the bioavailability of orally administered epothilones which comprises:

(i) a first component comprising one or more epothilones of Formula:



5

10 G is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo,



W is O or NR₁₆;

X is O; S; CHR₁₇; or H, R₁₈

15 Y is selected from the group consisting of O; H, H; H, OR₂₂; OR₂₃, OR₂₃; NOR₂₄; H, NOR₂₅; H, HNR₂₆R₂₇; NHNR₂₈R₂₉; H, NHNR₃₀R₃₁ or CHR₃₂, where OR₂₃, OR₂₃ can be a cyclic ketal;

B₁ and B₂ are selected from the group consisting of H, OR₃₃, OCOR₃₄, OCONR₃₅R₃₆, NR₃₇R₃₈, or NR₃₉CONR₄₀R₄₁

20 D is selected from the group consisting of NR₄₂R₄₃ or heterocyclo;

R₁, R₂, R₃, R₄, and R₅ are selected from H, lower alkyl;

R₈, R₉, R₁₀ and R₁₁ are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo or substituted heterocyclo;

5 R₁₇, R₁₈, R₂₂, and R₂₃ are selected from the group consisting of H, alkyl, and substituted alkyl;

R₂₄, R₂₅, R₂₆, R₂₈, R₃₀, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₃₉, R₄₀, R₄₁, R₄₂, R₅₁, R₅₂, R₅₃, and R₆₁ are selected from the group of H, alkyl, substituted alkyl, aryl or substituted aryl;

10 R₁₂, R₁₆, R₂₇, R₂₉, R₃₁, R₃₈, and R₄₃, are selected from the group consisting of H, alkyl, substituted alkyl, substituted aryl, cycloalkyl, heterocyclo, R₅₁C=O, R₅₂OC=O, R₅₃SO₂, hydroxy, and O-alkyl or O-substituted alkyl; or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof; and

(ii) a second component comprising a pharmaceutically acceptable acid neutralizing buffer,

15 wherein the first component and the second component are provided as an oral dosage form or as a pharmaceutical composition that can be reconstituted with a solvent to provide a liquid oral dosage.

21. The kit of claim 20, wherein at least one of the first component or the second
20 component is provided as a solid oral dosage form.

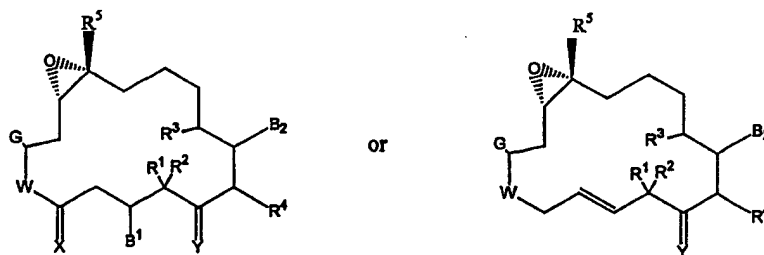
22. The kit of claim 21, wherein at least one of the first component or the second component is anhydrous.

25 23. The kit of claim 20, wherein at least one of the first component or the second component is provided as a pharmaceutical composition that can be reconstituted with a solvent to provide a liquid oral dosage form.

24. The kit of claim 23, wherein at least one of the first component or the second
30 component is provided as a tablet.

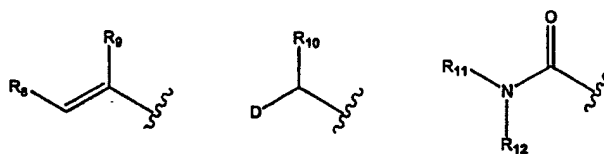
25. The kit of claim 23, wherein at least one of the first component or the second component is anhydrous.
26. The kit of claim 23, further comprising solvents for reconstituting the first or
5 second components.
27. The kit of claim 26, wherein the solvent for reconstituting the first component is a mixture of propylene glycol and ethanol.
- 10 28. A pharmaceutical composition suitable for oral administration to a mammal comprising:

(i) one or more epothilones of Formula:



wherein:

- 15 G is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo,



W is O or NR¹⁶;

X is O; S; CHR₁₇; or H, R₁₈;

- 20 Y is selected from the group consisting of O; H, H; H, OR₂₂; OR₂₃, OR₂₃; NOR₂₄; H, NOR₂₅; H, HNR₂₆R₂₇; NHNR₂₈R₂₉; H, NHNR₃₀R₃₁ or CHR₃₂, where OR₂₃, OR₂₃ can be a cyclic ketal;

B₁ and B₂ are selected from the group consisting of H, OR₃₃, OCOR₃₄, OCONR₃₅R₃₆, NR₃₇R₃₈, or NR₃₉CONR₄₀R₄₁

D is selected from the group consisting of NR_4R_3 or heterocyclo;

R_1 , R_2 , R_3 , R_4 , and R_5 are selected from H, lower alkyl;

R_8 , R_9 , R_{10} and R_{11} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo or substituted heterocyclo;

R_{17} , R_{18} , R_{22} , and R_{23} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{24} , R_{25} , R_{26} , R_{28} , R_{30} , R_{32} , R_{33} , R_{34} , R_{35} , R_{36} , R_{37} , R_{39} , R_{40} , R_{41} , R_{42} , R_{51} , R_{52} , R_{53} , and R_{61} are selected from the group of H, alkyl, substituted alkyl, aryl or substituted aryl;

R_{12} , R_{16} , R_{27} , R_{29} , R_{31} , R_{38} , and R_{43} , are selected from the group consisting of H, alkyl, substituted alkyl, substituted aryl, cycloalkyl, heterocyclo, $\text{R}_{51}\text{C}=\text{O}$, $\text{R}_{52}\text{OC}=\text{O}$, R_{53}SO_2 , hydroxy, and O-alkyl or O-substituted alkyl;

or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof, in solid form; and

(ii) a solid pharmaceutically acceptable acid neutralizing buffer in an amount sufficient to reduce decomposition of the one or more epothilones, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof when the pharmaceutical composition is reconstituted with a solvent to provide a liquid oral dosage form.

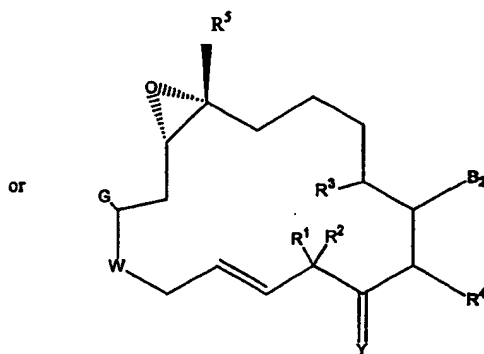
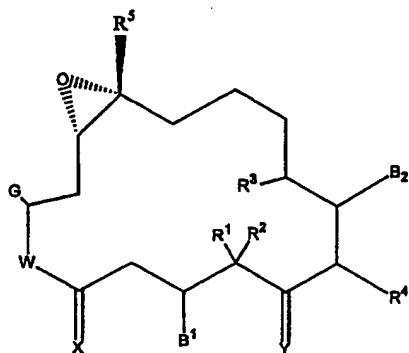
29. The pharmaceutical composition of claim 28, wherein the pharmaceutically acceptable acid neutralizing buffer provides a liquid oral dosage form having a pH between about 5 to 9.

30. The pharmaceutical composition of claim 28, wherein the pharmaceutically acceptable acid neutralizing buffer is present in an amount sufficient to provide at least about 20 milliequivalents of acid neutralization capacity.

31. The pharmaceutical composition of claim 28, wherein the pharmaceutically acceptable acid neutralizing buffer is a dibasic phosphate-citric acid-citrate buffer.

32. The pharmaceutical composition of claim 28, wherein the one or more epothilones or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof is present in an amount of between about 0.05 and 200 mg.
- 5 33. The pharmaceutical composition of claim 28, wherein the epothilone is [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 16S*]]-7, 11-dihydroxy 8, 8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5, 9-dione.
- 10 34. A kit comprising the pharmaceutical composition of claim 28 and a solvent for reconstituting the pharmaceutical composition to provide an oral dosage form.
35. The kit of claim 34, wherein the solvent comprises propylene glycol, ethanol, and phosphate buffer (1M, pH 8).
- 15 36. The kit of claim 35, wherein the ratio of propylene glycol:ethanol:phosphate buffer is about 58:12:30.
37. A liquid oral dosage form suitable for oral administration to a mammal
- 20 comprising:

(i) one or more epothilones of Formula:

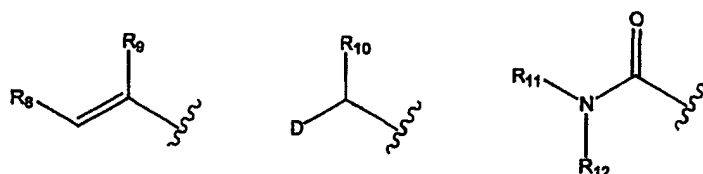


25

wherein:

G is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo,

5



W is O or NR₁₆;

10 X is O; S; CHR₁₇; or H, R₁₈;

Y is selected from the group consisting of O; H, H; H, OR₂₂; OR₂₃, OR₂₃; NOR₂₄; H, NOR₂₅; H, HNR₂₆R₂₇; NHNR₂₈R₂₉; H, NHNR₃₀R₃₁ or CHR₃₂, where OR₂₃, OR₂₃ can be a cyclic ketal;

B₁ and B₂ are selected from the group consisting of H, OR₃₃, OCOR₃₄,
15 OCONR₃₅R₃₆, NR₃₇R₃₈, or NR₃₉CONR₄₀R₄₁

D is selected from the group consisting of NR₄₂R₄₃ or heterocyclo;

R₁, R₂, R₃, R₄, and R₅ are selected from H, lower alkyl;

R₈, R₉, R₁₀ and R₁₁ are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo or substituted
20 heterocyclo;

R₁₇, R₁₈, R₂₂, and R₂₃ are selected from the group consisting of H, alkyl, and substituted alkyl;

R₂₄, R₂₅, R₂₆, R₂₈, R₃₀, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₃₉, R₄₀, R₄₁, R₄₂, R₅₁, R₅₂, R₅₃, and R₆₁ are selected from the group of H, alkyl, substituted alkyl, aryl or
25 substituted aryl;

R₁₂, R₁₆, R₂₇, R₂₉, R₃₁, R₃₈, and R₄₃, are selected from the group consisting of H, alkyl, substituted alkyl, substituted aryl, cycloalkyl, heterocyclo, R₅₁C=O, R₅₂OC=O, R₅₃SO₂, hydroxy, and O-alkyl or O-substituted alkyl;

or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof; and

(ii) a pharmaceutically acceptable liquid carrier.

- 5 38. The liquid oral dosage form of claim 41, wherein the epothilone is [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 16S*]]-7, 11-dihydroxy 8, 8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl-17-oxa-4-azabicyclo[14.1.0]heptadecane-5, 9-dione.
- 10 39. The liquid oral dosage form of claim 37, further comprising a pharmaceutically acceptable acid neutralizing buffer in an amount sufficient to reduce decomposition of the one or more epothilones, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof compared to a pharmaceutical composition without the buffer.
- 15 40. The liquid oral dosage form of claim 39, wherein the pH of the liquid oral dosage form is between about 5 to 9.
41. The liquid oral dosage form of claim 39, wherein the buffer is present in an amount sufficient to provide at least about 20 milliequivalents of acid neutralization capacity.
- 20 42. The liquid oral dosage form of claim 37, wherein the solvent is propylene glycol, ethanol, and water buffered with a phosphate buffer at pH about 8.
- 25 43. The liquid oral dosage form of claim 42, wherein the propylene glycol, ethanol, and water buffered with a phosphate buffer are present in a ratio of about 58:12:30.
- 30 44. The liquid oral dosage form of claim 42, wherein the epothilone is [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 16S*]]-7, 11-dihydroxy 8, 8,10,12,16-pentamethyl-3-[1-

methyl-2-(2-methyl-4-thiazolyl)ethenyl-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione.

45. The liquid oral dosage form of claim 37, wherein the one or more epothilones or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof is present in an amount of between about 0.05 and 200 mg.

46. The liquid oral dosage form of claim 39, wherein the buffer is dibasic phosphate-citric acid-citrate buffer.

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47. An article of manufacture which comprises:

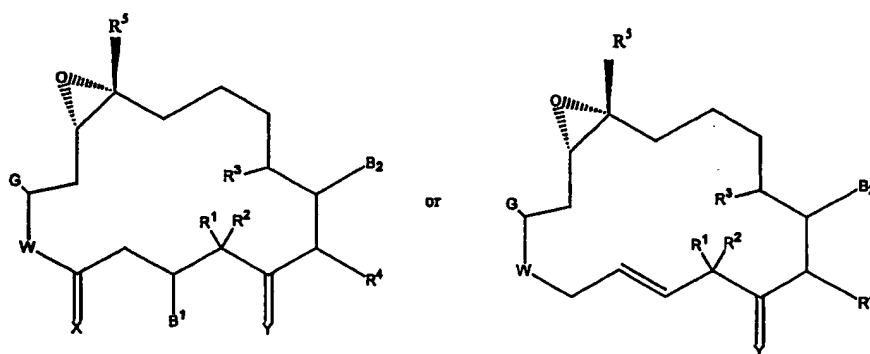
- (a) a sealable container suitable to carry a liquid or solid pharmaceutical;
- (b) one or more epothilones or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof; and

15 (c) a pharmaceutically acceptable carrier suitable to deliver the epothilone orally

48. A dispersible buffered tablet which comprises:

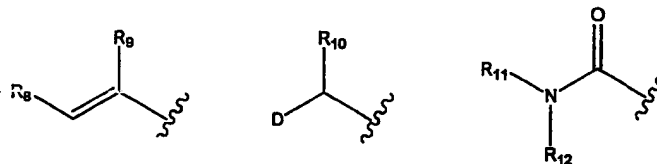
- (i) one or more epothilones of Formula:

20



wherein:

G is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo,



W is O or NR_{16} ;

X is O; S; CHR_{17} ; or H, R_{18} ;

- 5 Y is selected from the group consisting of O; H, H; H, OR_{22} ; OR_{23} , OR_{23} ; NOR_{24} ; H, NOR_{25} ; H, $HNR_{26}R_{27}$; $NHNR_{28}R_{29}$; H, $NHNR_{30}R_{31}$ or CHR_{32} , where OR_{23} , OR_{23} can be a cyclic ketal;

B_1 and B_2 are selected from the group consisting of H, OR_{33} , $OCOR_{34}$, $OCONR_{35}R_{36}$, $NR_{37}R_{38}$, or $NR_{39}CONR_{40}R_{41}$

- 10 D is selected from the group consisting of $NR_{42}R_{43}$ or heterocyclo;

R_1 , R_2 , R_3 , R_4 , and R_5 are selected from H, lower alkyl;

R_8 , R_9 , R_{10} and R_{11} are selected from the group consisting of, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo or substituted heterocyclo;

- 15 R_{17} , R_{18} , R_{22} , and R_{23} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{24} , R_{25} , R_{26} , R_{28} , R_{30} , R_{32} , R_{33} , R_{34} , R_{35} , R_{36} , R_{37} , R_{39} , R_{40} , R_{41} , R_{42} , R_{51} , R_{52} , R_{53} , and R_{61} are selected from the group of H, alkyl, substituted alkyl, aryl or substituted aryl;

- 20 R_{12} , R_{16} , R_{27} , R_{29} , R_{31} , R_{38} , and R_{43} , are selected from the group consisting of H, alkyl, substituted alkyl, substituted aryl, cycloalkyl, heterocyclo, $R_{51}C=O$, $R_{52}OC=O$, $R_{53}SO_2$, hydroxy, and O-alkyl or O-substituted alkyl;

or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof; and

- 25 (ii) buffer components which are suitable to neutralize gastric fluids for a time sufficient to allow said epothilone to be absorbed.

49. The kit of claim 20, wherein the first and second component is provided as a liquid oral dosage form.

50. The kit of claim 49, wherein the one or more epothilones or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof is present in an amount of between about 0.05 and 200 mg and the pharmaceutically acceptable acid neutralizing buffer is present in an amount sufficient to provide at least about 20 milliequivalents of acid neutralization capacity.

51. The kit of claim 20, wherein the first component and the second component is provided as a pharmaceutical composition that can be reconstituted with a solvent to provide a liquid oral dosage form; the one or more epothilones or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof is present as a in an amount of between about 0.05 and 200 mg; and the pharmaceutically acceptable acid neutralizing buffer is present in an amount sufficient to provide at least about 20 milliequivalents of acid neutralization capacity.

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52. The kit of claim 20, wherein the epothilone is [1S-[1R*, 3R*(E), 7R*, 10S*, 11R*, 16S*]]-7, 11-dihydroxy 8, 8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl-17-oxa-4-azabicyclo[14.1.0]heptadecane-5, 9-dione and the pharmaceutically acceptable acid neutralizing buffer comprises dibasic sodium phosphate, sodium citrate, and anhydrous citric acid.

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INTERNATIONAL SEARCH REPORT

PCT/US 02/01693

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/425 A61K47/12 A61K47/02 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 43320 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH)) 2 September 1999 (1999-09-02) abstract page 31, line 31 -page 32, line 28 page 33, line 11 - line 21 claims 1-52	1-52
A	WO 99 01124 A (SLOAN KETTERING INST CANCER) 14 January 1999 (1999-01-14) abstract page 1, line 37 - line 45 claims 1-58	1-52

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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